Abnormal serum pancreatic enzymes, but not pancreatitis, are associated with an increased risk of malignancy in patients with intraductal papillary mucinous neoplasms

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Introduction. *Pancreatitis is associated with intraductal papillary mucinous neoplasm (IPMN). This association is in part due to inflammation from pancreatic ductal obstruction. Although the correlation between pancreatitis and the malignant potential of IPMN is unclear, the 2012 International Consensus Guidelines (ICG) consider pancreatitis a "worrisome feature." We hypothesized that serum pancreatic enzymes, markers of inflammation, are a better predictor of malignancy than pancreatitis in patients with IPMN.*

Methods. *Between 1992 and 2012, 364 patients underwent resection for IPMN at a single university hospital. In the past decade, serum amylase and lipase were collected prospectively as an inflammatory marker in 203 patients with IPMN at initial surveillance and "cyst clinic" visits. The latest serum pancreatic enzyme values within 3 months preoperatively were studied. Pancreatitis was defined according to the 2012 revision of the Atlanta Consensus.*

Results. *Of the 203 eligible patients, there were 76 with pancreatitis. Pancreatitis was not associated with an increased rate of malignancy (*$P = .51$*) or invasiveness (*$P = .08$*). Serum pancreatic enzymes categorically outside of normal range (high or low) were also not associated with malignancy or invasiveness. In contrast, as a continuous variable, the higher the serum pancreatic enzymes were, the greater the rate of invasive IPMN. Of the 127 remaining patients without pancreatitis, serum pancreatic enzymes outside of normal range (low and high) were each associated with a greater rate of malignancy (*$P < .0001$ *and* $P = .0009$*, respectively). Serum pancreatic enzyme levels above normal range (high) were associated with a greater rate of invasiveness (*$P = .02$*).*

Conclusion. *In patients with IPMN without a history of pancreatitis, serum pancreatic enzymes outside of the normal range are associated with a greater risk of malignancy. In patients with a history of pancreatitis, there is a positive correlation between the levels of serum pancreatic enzymes and the presence of invasive IPMN. These data suggest serum pancreatic enzymes may be useful markers in stratification of pancreatic cancer risk in patients with IPMN. (Surgery 2014;156:923-30.)*

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When Ohashi and colleagues[1] first described intraductal papillary mucinous neoplasm (IPMN) in a case report 22 years ago, it was considered an unusual entity. Today, because of improved imaging techniques and better awareness among physicians, IPMN accounts for 20–70% of all cystic neoplasms of the pancreas and is the main indication for pancreatic resection (10–20% of all pancreatectomies).[2] IPMN is a well-established precancerous pancreatic lesion with a stepwise progression from low-grade dysplasia to high-grade dysplasia (formerly carcinoma in situ) and finally invasive

carcinoma, similar to colonic polyps in colon adenocarcinoma.[3,4]

For invasive pancreatic adenocarcinoma, a delayed presentation, low resectability rate, aggressive tumor biology, and absence of effective systemic treatment result in a poor prognosis and an overall 5-year survival of 5%.[5] IPMN represents a potential "window of opportunity" for pancreatic cancer prevention and early detection. Management of IPMN has fundamentally changed over the past 2 decades. After its early description, surgical resection was pursued for many patients with IPMN simply because of its indeterminate but potential malignant risk. IPMN surgical pathology, however, revealed low- to moderate-grade dysplasia in the majority of patients. Thus, some of these patients could have theoretically avoided surgical resection.

In 2006 and 2012, the International Association of Pancreatology published consensus guidelines[3,4] to help address the dilemma of "over" versus "under" treatment of IPMN and define indications for resection by stratifying patients based on criteria suspicious for malignant progression ("worrisome features" and "high-risk stigmata"). Acute pancreatitis is the most common condition associated with IPMN. It is the presenting complaint in 10–15% of patients with IPMN, and one-third of patients with IPMN have at least some documented history of acute pancreatitis.[6] IPMN is a well-known etiology for acute pancreatitis with the pathophysiology of inflammation thought to be in part due to ductal hypertension caused by excessive mucin production.[6,7]

Several studies have compared the rate of acute pancreatitis in non-malignant and malignant IPMN with quite variable results. In some surgical series, acute pancreatitis is protective, whereas in others, acute pancreatitis is a predictor of malignant progression. Most series, however, found no difference. Despite the lack of a clear association, the 2012 International Consensus Guidelines consider acute pancreatitis a "worrisome feature" for patients with IPMN.[4] We hypothesized that serum pancreatic enzymes, markers of inflammation and pancreatic functional reserve, are a better predictor of malignancy than pancreatitis in patients with IPMN.

METHODS

Patient selection. Between 1992 and 2012, data from all patients who underwent resection of IPMN at a single academic institution were reviewed. A retrospective analysis of a prospectively collected database, supplemented by review of the electronic medical records, was performed. Data were collected and reported in strict compliance with patient confidentiality guidelines defined by the Indiana University Institutional Review Board.

Table I. Patients' classification according to serum amylase and serum lipase values

Serum amylase level	*Serum lipase level*	*Number of patients (%)*	*Final category*	*Number of patients in each category (%)*
Low	Low	6 (3%)	Low	41 (21%)
Low	Normal	5 (3%)		
Normal	Low	30 (15%)		
Normal	Normal	84 (41%)	Normal	84 (41%)
Normal	High	25 (12%)	High	78 (38%)
High	Normal	7 (3%)		
High	High	46 (23%)		

Normal serum amylase range: 25–125 U/L; low is <25 U/L; high is >125 U/L.
Normal serum lipase range: 22–51 U/L; low is <22 U/L; high is >51 U/L.

Parameters assessed. A history of acute pancreatitis was assessed by in-person interview at the time of a clinic visit and/or by review of the patient's medical record (clinic notes, imaging studies, and laboratory results). Acute pancreatitis was defined according to the 2012 revision of the Atlanta classification[8] as the presence of two of the following three features: abdominal pain consistent with acute pancreatitis (acute onset of persistent, severe, epigastric pain often radiating to the back); serum lipase activity (or amylase activity) at least 3 times greater than the upper limit of normal; and/or characteristic findings of acute pancreatitis on imaging studies (contrast-enhanced computed tomography, magnetic resonance imaging, or transabdominal ultrasonography).

In the past 10 years, serum pancreatic enzymes levels (serum amylase and lipase) were collected prospectively as an inflammatory marker in IPMN patients at initial and surveillance visits at the Pancreatic Cyst and Cancer Early Detection Center. Normal ranges were defined according to the values established by Indiana University Health Center laboratory as an amylase serum activity between 25 and 125 U/L and a lipase serum activity between 22 and 51 U/L. Serum pancreatic enzyme levels were classified into 3 categories: normal, low (ie, outside the normal range being less than normal) and high (ie, outside the normal range being greater than normal). The classification scheme used for this study is described in Table I. Of note, no patient in our cohort had discrepancy between serum amylase and serum lipase (one value greater than normal range vs one value less than normal range). The latest documented serum